REMARKS

Claims 1, 10-11, 15 and 29-30 are pending in the application.

Claims 1, 10-11, 15 , 29 and 30 have been rejected under 35 USC 103(a) as allegedly unpatentable over Solomou, et al., Weintraub, Monia et al., Symonds et al. and Gruenberg et al. Applicants respectfully traverse this rejection.

The present invention is directed to a method of increasing IL-2 production in lymphocytes or T cells in a patient in vivo (claims 1, 10, 11, 15) or ex vivo (claims 29 and 30). Normal IL-2 production in T Cells is important. T Cells from patients with SLE have a greatly reduced production of IL-2. Applicants have shown and claimed that the introduction of anti-sense CREM into lymphocytes from a patient with SLE operates to decrease CREM production and additionally, to increase IL-2 production in the T Cells (see Fig. 3, 5A and 6). Applicants have shown that treating with antisense CREM enhances the activity of the IL-2 promoter (Fig. 4, 4A, 4B, 4C, 5A).

None of the cited references, whether taken alone or in combination, provide the necessary teaching to motivate one of ordinary skill in the art to arrive at the present invention.

Solomou, et al. is a paper that was written by the present inventor. This paper reports the discovery of CREM as being the culprit for decreased IL-2 production. However, this was very early work and it was not known at that time how to alleviate or resolve the problem.

Weintraub is directed to basic teachings that molecules that bind with specific mRNA can selectively turn off genes. Weintraub refers to the use of silencing RNAs (sRNA) to silence the expression of specific RNAs and speculates that this may someday be useful technology. Weintraub is very general in its teachings. It only speculates that

viral diseases or *dangerously mutated oncogenes* might be treated. (page 45 upper left column). Notably, it does not suggest that diseases wherein defective genes are present in lymphocytes or other naturally occurring cells of the human body could be treated. It also does not provide any guidance on whether such treatment would even be harmful to patients in vivo. With the limited teachings in Weintraub, it would have been too large of a leap in science at the time of the invention to speculate that the "silencing RNA" of Weintraub that have only been associated with viral disease or oncogenes would operate the same way in T-cells that are part of the immune system. The type of cells are so different that one could not speculate that the antisense CREM would be effective in lymphocytes. There is also no suggestion of what primers would work for producing antisense CREM. Weintraub simply does not indicate how to solve the problem that Solomou defines. There is no way to determine or predict that the methods in Weintraub would increase IL-2 production in humans that would result in benefiting SLE patients.

Monia et al. deals with antisense modulation of SMAD7 expression. SMAD 7 was isolated from cultured human vascular endothelial cells. SMAD7 regulates modulating endothelial gene expression. Endothelial cells are totally different than T-cells described by Solomou or the present invention. T-cells function to solve complex immunology problems. There is no disclosure or suggestion of whether this method would be useful in Solomou's T-cells or would have any affect on IL-2 production. There is also no suggestion that antisense technology is effective for all types of cells which would be needed to make up for the deficiency of Weintraub. There is also no disclosure or suggestion of whether or not administering gene-modified T cells treated with antisense cAMP response element modulator plasmid would actually increase the

production of IL-2 in patients with SLE in vivo or whether other factors would exist that would affect IL-2 production. There is no disclosure of what primers would be needed. Therefore, Monia does not assist one of ordinary skill in the art to complete the puzzle that Solomou or Weintraub leave uncompleted.

Symonds et al. proposes transfection of CD34 proginitor cells (not terminally differentiated T cells in solomou or the present invention). The proginator cells are very difficult to gene modify. Symonds et al. , like Weintraub and Monia, is not directed to the claimed highly complex immunological T cells.

By citing Weintraub, Monia and Symonds et al, the Examiner has asserted that gene therapy using antisense is relatively simple to effectuate. Nothing could be further from the truth. However, it was known in the art at the time of the invention that despite the early promise of gene therapy, there has been little success despite massive efforts in the last decade. This is due at least in part to low efficiencies of gene transfer, an inability to modify enough cells, an inability to target appropriate cell types, and a lack of persistence of the desired effect in human subjects. (Symonds, Column 1, lines 54-60). In light of this problem, Symonds leads the artisan to believe that the solution to SLE is not easy. Symonds does not indicate how to modify the teachings of Weintraub or Mania to provide a procedure that could be expected to produce successful results including high efficiencies of gene transfer in T cells. Therefore, the combination of references does not present a reasonable expectation of success given the state of the art.

Gruenberg is the only reference cited by the Examiner that relates to T-Cells. In Gruenberg, they stimulates T cells in vitro with polyclonal stimulators (CD3, CD28). Unlike the present invention, Gruenberg operates without any growth factors like IL-2 or

IFN-γ present. Also unlike the present invention, Gruenberg frequently restimulates T cells or T cell subset with immobilized anti-CD3 and anti-CD28 mAb to cause them to proliferate and differentiate into a highly pure population of activated memory Th1 cells. The restimulation must be every 2-3 days and the restimulation must be repeated at least 3 and typically 4 times in order to obtain a pure population of activated Th1 memory cells. Activation with these antibodies greater than 5 times, however, results in diminishing cytokine production and increased activation-induced cell death. (page 2, paragraph 0017). Gruenberg's approach is that of polyclonal activation in vitro and although it may increase Th1 cytokines, the response varies from individual to individual and, therefore, is unpredictable. It is very different than the present invention. Gruenberg clarifies that the present invention is not simple science but an invention that really required extraordinary experimentation and testing to discover a cure for SLE.

The presently claimed invention silences a protein in T cells obtained from patients with SLE using in vitro gene transfer in order to specifically increase IL-2 production. It corrects the T-cells not just activates them. There is absolutely no overlap of the claimed invention and Gruenberg. Gruenberg does, however, demonstrate the difficulty experienced in the art of studying T cells. It also demonstrates the difficulty in working with the genetic mechanisms in T cells (increased activation-induced cell death).

Although a person of ordinary skill in the art would have appreciated from Solomou et al. that it is desirable to increase IL-2 production in SLE patients and that CREM causes decreased IL-2 production, neither it or the other references of Weintraub, Monia e tal, Symonds et al. or Gruenberg provide any guidance to the skilled artisan on how to modify T cells with antisense CREM in such a way that they will actually

increase IL-2 production or whether it would even work. Therefore, the invention is more than the predictable use of prior art elements according to their established functions. As shown from Gruenberg, such variables as the frequency of treatment can greatly affect cell death.

There are many variables related to the conditions required for the inhibition of a particular gene including the type of cell (T-Cell) in which the gene is present, the type of vector used, the modifying conditions, etc. What the inventors have claimed is not the product of routine research and it is not a simple upgrade of methods known in the art. Thousands suffer from SLE and no cure has yet been found. The inventors, through years of work and trial and error have discovered the claimed method. It is respectfully submitted that this rejection is overcome. The Examiner's combination of references is based on hindsight. It is 2008 and this therapy has not been accomplished and is still not available or published. This alone is evidence of the uncertainty and unpredictability of *successful* gene therapy.

Reconsideration is respectfully requested.

Respectfully submitted,

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